CBP/catenin antagonist safely eliminates drug-resistant leukemia-initiating cells.

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Public Summary:
The results from these studies demonstrate that specifically antagonizing the CREB-binding protein/catenin interaction with ICG-001 (a small molecule inhibitor) can eliminate drug-resistant chronic myelogenous leukemia-leukemia-initiating cells without deleterious effects to the normal endogenous hematopoietic stem cell population.

Scientific Abstract:
CREB-binding protein (CBP) and p300 are highly homologous transcriptional coactivators with unique, non-redundant roles that bind a wide array of proteins, including catenins-beta and gamma. ICG-001 is a small-molecule inhibitor that specifically inhibits the CBP/catenin interaction. Importantly, ICG-001 does not inhibit the p300/catenin interaction. We demonstrate that specifically inhibiting the interaction between CBP and catenin with ICG-001 results in the differentiation of quiescent drug-resistant chronic myelogenous leukemia-initiating cells (CML LICs), thereby sensitizing them to BCR-ABL tyrosine kinase inhibitors, for example, Imatinib. Using ICG-001 in a NOD/SCID/IL2Rgamma-/- mouse model of engrafted human chronic myelogenous leukemia, we now demonstrate the complete elimination of engrafted leukemia after only one course of combined chemotherapy. Combination-treated animals live as long as their non-engrafted littermates. Results from these studies demonstrate that specifically antagonizing the CBP/catenin interaction with ICG-001 can eliminate drug-resistant CML LICs without deleterious effects to the normal endogenous hematopoietic stem cell population.Oncogene advance online publication, 14 December 2015; doi:10.1038/onc.2015.438.